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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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07/871,997 04/24/92 WEI FANG

2303 2A

EXAMINER

NEFF, D

ART UNIT

PAPER NUMBER

1808

DATE MAILED:

07/15/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/24/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 35-41 + 53-62 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 35-41 + 53-62 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The information disclosure statements filed 8/3/92 and 1/19/93 fail to comply with the provisions of MPEP 609 because
5 the statements have been filed after the first office action and do not contain a certification as specified in 37 CFR 1.97(e) or a fee as set forth in 37 CFR 1.17(p). They have been placed in the application file, but the information referred to therein has not been considered as to the merits. The statement of 1/19/93
10 has been considered to the extent of applicants arguing that it teaches away from the invention. Moreover, form PTO-1449 attached to the statement of 8/3/92 duplicates the same form submitted in parent application Serial No. 07/387,003. The references listed on this form were considered in the parent
15 application and the parent application is part of the present file wrapper continuation. Contrary to the assertion in the disclosure statement, the statement was not filed within three months of the filing date of the present application since the statement was filed on 8/3/92 and the filing date is 4/24/92.

20 Claims 1, 35-39 and 53-62 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a buffer as required by claim 40 for reasons set forth in the previous office action of 7/15/92. See M.P.E.P. §§ 706.03(n) and 706.03(z).

25 Applicants assert that the specification at page 24, beginning at line 21, supports the invention of claim 1 that is broader than the invention of claim 40. However, the broader

disclosure in the specification is merely a general outline of the invention and does not provide description of a working embodiment. There is inadequate support in the specification that the invention as outlined by the general description can be
5 a working embodiment and there is inadequate support in the specification for obtaining utility with a composition containing only the enzyme and any nonionic detergent. The only working embodiment of a storage buffer that has been used and found to provide the desired results is that required by claim 40 and
10 described in the working examples in the specification. Biochemical reactions are unpredictable and it would be unpredictable as to results that would be obtained when performing the invention substantially different than actually carried out.

15 Claims 1, 35-39 and 53-59 are rejected under 35 U.S.C. § 102(a) as being anticipated by the MBR product information sheet for reasons set forth in the previous office action of 7/15/92 in this application and the office actions of 9/4/90 and 5/3/91 in parent application Serial No. 07/387,003.

20 Applicants urge that the 37 CFR §1.131 Declaration of 4/21/92 should establish priority of the invention since In re Wilkinson 134 USPQ 171 and In re Moore 170 USPQ 260 hold that the applicant need not be required to show any more acts with regard to the subject matter claimed than can be carried out by one of
25 ordinary skill in the pertinent art following the description contained in the reference. However, the declaration does not demonstrate that applicants were in possession of the MBR buffer

prior to 6/8/87. As set forth in the previous office action, the MBR buffer is different from the 2X storage buffer according to the invention prior to 6/8/87 as set forth in the declaration. The MBR buffer is also different from the buffer described as a
5 working embodiment in the present specification. The present claims encompass the MBR buffer and are not limited to the buffer asserted by the declaration to be before 6/8/87.

The 37 CFR §1.131 Declaration of 1/6/93 is unpersuasive for the type of reasons set forth above. Applicants urge that
10 exhibit C (page 101) of this declaration and experiment 3 of the Akers Declaration demonstrate that gelatin is not an enzyme stabilizer since enzyme activity decreased in the presence of gelatin when a nonionic detergent is not present. However, if the gelatin had not been present, the enzyme activity may have
15 decreased even faster. In any event, gelatin must provide an important function in combination with a nonionic detergent in a storage buffer since the storage buffer specifically exemplified in the specification contains gelatin. There is nothing in the specification to indicate that gelatin can be omitted from the
20 specific storage buffer described in example XIV on page 79. No specific storage buffer has been described in the specification not containing all the components of claim 40. While page 57 of exhibit D discloses a storage buffer containing all the
25 exhibit is not part of the specification and cannot put subject matter into the specification that is not originally disclosed therein. When the specification was filed, it was apparently

believed that gelatin should be present in the storage buffer since a specific storage buffer as in exhibit D without gelatin is not described in the specification. The beneficial effect of gelatin is further supported by Kaledin et al(81)(page 1250,
5 section 4) and Kaledin et al(80)(page 497, 4th paragraph) disclosing that gelatin is necessary to stabilize the enzyme.

Applicants assert that applying Goff et al or Spiegelman and Feller et al under 35 USC § 102 is improper. However, these references were not applied under 102. They were merely referred
10 to in responding to applicants' arguments to show that MBR could have obtained suggestion of using a nonionic buffer to stabilize the enzyme without relying on the Cetus protocol.

Claims 60-62 are rejected under 35 U.S.C. § 103 as being unpatentable over the product information sheet of MBR for
15 reasons set forth in the previous office action of 7/15/92 in this application and the above noted previous office actions in the parent application.

The comments set forth above also apply to arguments concerning this rejection. Applicants have not pointed why the
20 specific limitations of these claims are unobvious over the limitations of the claims rejected above.

Claims 1, 35-39, 53-59 and 62 are rejected under 35 U.S.C. § 103 as being unpatentable over Kaledin et al(80) in view of Goff et al and, if necessary, in further view of Feller et al or
25 Spiegelman for reasons set forth in the previous office action of 7/15/92 in this application and the above noted previous office actions in the parent application.

Applicants assert that the claims require a purified enzyme whereas the preparation of Kaledin et al is crude. However, it appears that Kaledin et al disclose a purified enzyme in addition to a crude enzyme. See Table 1 on page 495 where purification is carried out by ammonium sulfate precipitation and by different chromatographic methods.

Applicants urge that Kaledin et al(81) disclose(page 1350, section 5) obtaining stability for 3 years without gelatin and therefore gelatin is not necessary for obtaining stability.

However, in section 5, elution is with buffer C and dialysis is against 50% glycerol in buffer C. Since buffer C contains gelatin, it appears the preparation stored for 3 years contained gelatin since it is additionally disclosed in section 4 on this page that gelatin is necessary for stability of the enzyme.

While the enzymes of Goff et al, Spiegelman and Feller et al may not be a thermostable DNA polymerase, the enzymes purified as disclosed by these references are DNA polymerases.

Spiegelman(col 2, line 4) and Feller et al(col 1, lines 67-68) disclose that DNA polymerase is a reverse transcriptase(RT). The DNA polymerases of the references are sufficiently similar to the thermostable DNA polymerase of the claims that it would be expected that a nonionic detergent would function to stabilize the thermostable DNA polymerase in view of its functioning to prevent loss RT activity as disclosed by Goff et al. While Spiegelman and Feller et al may be using the nonionic detergent to solubilize the enzyme, when Goff et al is considered, it would have been apparent that the detergent also functions to prevent

loss of enzyme activity. Moreover, it would have been obvious to use the detergent to maintain the enzyme soluble in a storage buffer and stability would have been inherent. The references are applied together and must be considered together as a whole.

5 Contrary to applicants' assertion, there is clearly motivation to use a nonionic detergent to stabilize the DNA polymerase of Kaledin et al(80). This motivation is provided by Goff et al disclosing(col 8, lines 20-25) that recovery of activity in the soluble fraction required the presence of
10 nonionic detergent and(col 20, lines 20-30) that the presence of nonionic detergent was required throughout the purification to prevent aggregation and loss of activity.

Contrary to applicants' argument, Goff et al is not merely preventing proteolytic degradation of fusion proteins. Goff et
15 al clearly disclose that the detergent prevents loss of activity during purification. Additionally, as shown by table 4(paragraph bridging cols 22 and 23), the detergent NP40 is present in a reaction mixture for determining activity of RT. If the detergent is required throughout purification and during activity
20 determination of RT, it would be clearly expected to be required during storage of an RT. The Akers Declaration does not refute this. Experiment 1 of the declaration does not establish that activity is not effected by presence or absence of nonionic detergent. Experiment 1 does not mention activity but states
25 that "functionality" appears to be equivalent whether or not the detergent is present. What is functionality? An enzyme that has reduced activity can still function. As stated in the previous

office action, the results of experiment 2 would have been expected in view of Goff et al. Moreover, as noted in the previous office action, experiments 2 and 3 require both NP-40 and Tween 20 and the claims do not require these detergents together. Also, the experiments require other components of claim 40. The claims must be commensurate in scope with the experiments carried out according to the invention. Experiment 3 also relates to functionality and not activity as disclosed by the references. Moreover, this experiment contradicts with the Kaledin et al references which disclose that gelatin is necessary to prevent loss of activity. There can be seen no reason to accept applicants' experiment as correct and the results of Kaledin et al as incorrect. The difference in amino acid sequence alleged in the Gelfand Declaration does not establish that RT and thermostable polymerase are unrelated as to stability problems. The fact that both are DNA polymerases clearly establishes that they are related enzymes. Enzymes with different amino acid sequences can be quite similar in function and in regard to factors that affect activity. Goff et al producing the RT by recombinant techniques does not make it unrelated to the thermostable DNA polymerase of Kaledin et al. The enzymes of Feller et al and Spiegelman are not recombinant and like Goff et al these references require the presence of a nonionic detergent when purifying the enzymes. The main difference is that one is thermostable and one may not be. This merely determines the temperature at which the enzyme functions.

Applicants assert that an article by Wu et al discloses that

nonionic detergents do not stimulate the activity of bacterial DNA polymerase. However, the tests of this reference were conducted only with the detergent, Triton X-100 (Table III). The RT isolated by Goff et al is from a bacteria and activity loss is inhibited with the detergent, NP-40. Thus, Goff et al suggest that the NP-40 would prevent the loss of activity of DNA polymerase from bacteria in a storage buffer. Moreover, the present invention as broadly claimed does not require the thermostable DNA polymerase to be from bacteria. Furthermore, the detergent would be expected to improve the solubility of bacteria DNA polymerase irrespective of whether better activity is expected.

Claims 60 and 61 are rejected under 35 U.S.C. § 103 as being unpatentable over the references as applied to claims 1, 35-39, 53-59 and 62 above, and further in view of Kaledin et al (1981) for reasons set forth in the previous office action of 7/15/92 in this application and the above noted office actions in the parent application.

Comments set forth above in response to applicants' arguments also apply to this rejection. As noted above, Kaledin et al (81) does not disclose that stability of 3 years is obtained without gelatin. On the contrary, gelatin is present since buffer C contains gelatin.

Claims 40 and 41 are allowable, however, the claims are objected to as being dependent on a rejected claim.

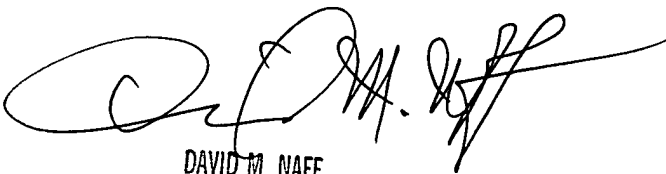
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

5 A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL
ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS
ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS
OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION
IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED
STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE
ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE
PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE
MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE
10 STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM
THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed
to Examiner Naff at telephone number (703) 308-0520.

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20 DMN
March 17, 1993


DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1808